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(54) **Novel anthranilamide pyridinureas as VEGF receptor kinase inhibitors**

(57) The invention relates to novel anthranilamide pyridinureas as VEGF receptor kinase inhibitors, their production and use as pharmaceutical agents for treating diseases that are triggered by persistent angiogenesis.

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Description

[0001] The invention relates to novel anthranilamide pyridinureas as VEGF receptor kinase inhibitors, their production and use as pharmaceutical agents for treating diseases that are triggered by persistent angiogenesis.

[0002] Many diseases are known to be associated with persistent angiogenesis, for example, diseases such as tumor- or metastases-growth; psoriasis; arthritis, such as rheumatoid arthritis, hemangioma, endometriosis, angiofibroma; eye diseases, such as diabetic retinopathy, neovascular glaucoma; renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell proliferative diseases and arteriosclerosis.

[0003] Lymphangiogenesis is a process accompanying tumor growth and metastases. It is prominent in lymphedema, lymphangiectasia, lymphangioma, and lymphangiosarcoma and in asthmatic disease, where lymph vessels are chronically overexpressed in the lung.

[0004] Persistent angiogenesis is induced by the factor VEGF via its receptors. In order for VEGF to exert this action, it is necessary that VEGF bind to the receptor, and that a tyrosine phosphorylation is induced.

[0005] Direct or indirect inhibition of the VEGF receptor can be used for treating such diseases and other VEGF-induced pathological angiogenesis and vascular permeable conditions, such as tumor vascularization. For example, it is known that the growth of tumors can be inhibited by soluble receptors and antibodies against VEGF, an example for the latter being Avastin® whose treatment paradigm has been introduced in human cancer therapy.

[0006] Anthranilic acid amides effective in the treatment of psoriasis; arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma; eye diseases, such as diabetic retinopathy, neovascular glaucoma; renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents, have been reported in WO 00/27820.

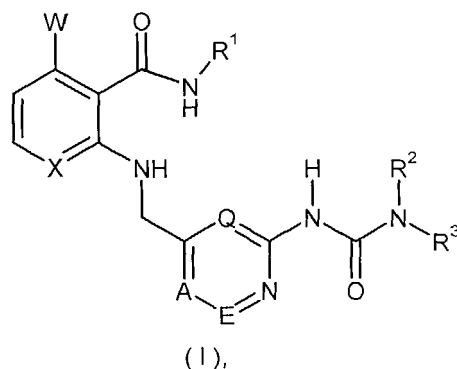
[0007] Anthranilic acid amides that are effective in the treatment of tumor or metastasis growth, psoriasis, Kaposi's sarcoma, restenosis, such as, e.g., stent-induced restenosis, endometriosis, Crohn's disease, Hodgkin's disease, leukemia; arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma; eye diseases, such as diabetic retinopathy, neovascular glaucoma; renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents, as immunosuppressive agents, as a support in scar-free healing, in senile keratosis and in contact dermatitis have also been reported in WO 04/13102.

[0008] There is, however, a desire to produce compounds that are as efficacious as possible in as broad a range of indications as possible. A constant blockade of VEGF mediated signal transduction is desirable in order to reduce persistent angiogenesis and lymphangiogenesis. Suitable compounds for longer term treatment should exhibit little or no drug-drug interaction potential. The Cytochrome P450 isoenzymes play a pivotal role in the degradation of pharmaceutical agents. The problem is also complicated by the fact that patients may express different relative amounts of the isoenzymes. An inhibition of these isoenzymes may result in undesirable pharmaceutical agent interactions, especially in the case of multimorbid patients (patients with multiple disease conditions). For example, inhibition of the Cytochrome P450 isoenzymes responsible for metabolism of the parent agent could lead to toxic systemic concentrations. A further problem exists in combination therapy with other medications, whereby inhibition of the Cytochrome P450 isoenzymes responsible for metabolising the co-medications could lead to toxic systemic concentrations of the co-medication. This is especially the case for co-administered cytostatics in the case of cancer therapy.

[0009] Thus, it has now surprisingly been found that compounds of general formula (I), as described below, have more advantageous physico-chemical and/or pharmacokinetic properties and prevent, for example, tyrosine phosphorylation or stop persistent angiogenesis and thus the growth and propagation of tumors, whereby they are distinguished in particular by a potent inhibition of VEGF receptor kinases and a reduced potential for drug-drug interactions, specifically a reduced inhibition of cytochrome P450 isoenzymes 2C9 and 2C 19.

[0010] The compounds of formula (I) are thus suitable, for example, for the treatment or prevention of diseases for which an inhibition of angiogenesis and/or the VEGF receptor kinases is beneficial.

[0011] In one aspect of the invention, there is provided an anthranilamide pyridinurea compound of formula (I):



wherein:

X is CH or N, preferably CH;

W is hydrogen or fluorine; preferably hydrogen;

A, E and Q independently of one another, are CH or N, whereby only a maximum of two nitrogen atoms are contained in the ring; preferably A, E, and Q are each CH;

R¹ is aryl or heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸; preferably heteroaryl optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸; more preferably heteroaryl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸; even more preferably quinolinyl, isoquinolinyl, or indazolyl which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸; even further preferred quinolinyl, isoquinolinyl, or indazolyl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸; most preferred indazolyl substituted with C₁-C₁₂-alkyl, particularly 2-methyl-indazolyl and 1-methyl indazolyl;

R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵; preferably R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which contains no or one further heteroatom, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl; preferably C₁-C₁₂-alkyl; most preferably -CH₃;

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl; preferably -CH₃ or hydrogen; most preferably hydrogen;

R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl, or -NR⁷R⁸; preferably C₁-C₁₂-alkyl or -NR⁷R⁸; most preferably -CH₃;

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl, or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; preferably R⁷ and R⁸ independently of one

another, are hydrogen, COR⁶, -SO₂R⁶, C₁-C₁₂-alkyl; more preferably hydrogen or C₁-C₁₂-alkyl; most preferably hydrogen or -CH₃,

and as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

[0012] In a second aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof.

[0013] In a third aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof and at least one pharmaceutically acceptable carrier, diluent or excipient.

[0014] In a fourth aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in the treatment of diseases associated with persistent angiogenesis and/or diseases associated with excessive lymphangiogenesis.

[0015] In a fifth aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in the treatment of tumor- or metastases-growth; psoriasis; Kaposi's sarcoma; restenosis including stent-induced restenosis; Crohn's disease; Hodgkin's disease; leukemia; arthritis including rheumatoid arthritis, hemangioma, angiofibroma; endometriosis; eye diseases including diabetic retinopathy, neovascular glaucoma; corneal transplants; renal diseases, including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, including cirrhosis of the liver; mesangial cell proliferative diseases; arteriosclerosis; injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment; in vascular prosthetics or after mechanical devices are used to keep vessels open, as immunosuppressive agent for supporting scar-free healing; senile keratosis; contact dermatitis; and asthma.

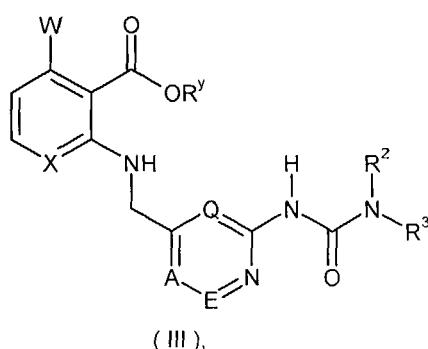
[0016] In a sixth aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use as VEGF receptor kinase 3-inhibitors of lymphangiogenesis.

[0017] In a seventh aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in a method for the treatment of the human or animal body.

[0018] In an eighth aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use in the preparation of a pharmaceutical product for the treatment of a disease for which an inhibition of angiogenesis and/or lymphangiogenesis and/or the VEGF receptor kinases is beneficial.

[0019] In a ninth aspect of the present invention, there is provided a pharmaceutical agent comprising at least one compound of formula (I) or an isomer, diastereoisomer, enantiomer, tautomer or salt thereof for use as an inhibitor of the tyrosine kinases VEGFR-1 and VEGFR-2.

[0020] In a tenth aspect of the present invention, there is provided a compound of general formula (III),



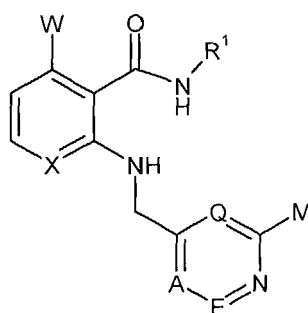
in which A, E, Q, W, X, R² and R³, are as defined in formula (I) and R^y is H or C₁-C₆-alkyl, as intermediate for the preparation of a compound of formula (I). Preferably R^y is H or C₁-C₂-alkyl, W is hydrogen and X is CH; most preferably R^y is H or -CH₃, W is hydrogen and X is CH.

[0021] In an eleventh aspect of the present invention, there is provided the use of a compound of general formula (III), in which A, E, Q, W, X, R² and R³ are as defined in formula (I) and R^y is H or C₁-C₆-alkyl, as intermediate for the preparation of a compound of formula (I).

[0022] In a twelfth aspect of the present invention, there is provided a process for the preparation of a compound of

formula (I), wherein all substituents are as described in claim 1, in which a compound of formula (III), wherein A, E, Q, W, X, R² and R³ are as defined in claim 1 and R^y is H or C₁-C₆-alkyl, is reacted with an amine of formula R¹NH₂ in which R¹ is as defined in claim 1.

[0023] In a thirteenth aspect of the present invention, there is provided a process for the preparation of a compound of formula (I), wherein all substituents are as described in claim 1, in which a compound of formula (II),



(II),

wherein A, E, Q, W, X, and R¹ are as defined in claim 1 and M stands for halogen, is:

- (i) first converted to an amine and subsequently converted to a compound of formula (I) by reaction with a carbamoyl chloride of formula CICONR²R³, wherein R² and R³ are as defined in claim 1; or alternatively,
- (ii) reacted with a compound of formula H₂NCONR²R³, wherein R² and R³ are as defined in claim 1, or alternatively,
- (iii) first converted to an amine and subsequently converted to a compound of formula (I) by first reacting with a compound of formula ClCO₂Ph and then reacting with a compound of formula HNR²R³, wherein R² and R³ are as defined in claim 1. Preferably a compound of formula (I) is prepared using the (ii) process.

[0024] As used herein, the term "alkyl" is defined in each case as a substituted or unsubstituted straight-chain or branched alkyl radical, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl or hexyl, heptyl, octyl, nonyl, decyl, undecyl, or dodecyl.

[0025] As used herein, the term "alkoxy" is defined in each case as a straight-chain or branched alkoxy radical, such as, for example, methyloxy, ethyloxy, propyloxy, isopropoxy, butyloxy, isobutyloxy, tert-butyloxy, pentyloxy, isopentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy, undecyloxy or dodecyloxy.

[0026] As used herein, the term "cycloalkyl" is defined as a monocyclic alkyl ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, and also as bicyclic rings or tricyclic rings, such as, for example, adamantanyl. The cycloalkyl radical may also contain, one or more heteroatoms, such as oxygen, sulfur and/or nitrogen, such that a heterocycloalkyl ring is formed.

[0027] As used herein, the term "heterocycloalkyl" is defined as a monocyclic alkyl ring which contains one or more heteroatoms, such as oxygen, sulfur and/or nitrogen. Preferred are 3-8 membered heterocycloalkyl rings. More preferred are 5 or 6 membered heterocycloalkyl rings. For example, the following heterocycloalkyl rings can be mentioned: tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, morpholine, piperazine and thiomorpholine. The heterocycloalkyl radical may be optionally substituted in one or more places in the same way or differently with, for example, halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -SR⁴, -SOR⁴ or -SO₂R⁶, -COR⁶, -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵. It is understood that the substitution on the heterocycloalkyl radical may take place on any one of the heterocycloalkyl radical's carbon atoms and/or on any one of the heterocycloalkyl radical's heteroatoms. Preferably the heterocycloalkyl radical is substituted in one or two places.

[0028] As used herein, the term "cycloalkenyl" is defined in each case as cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl or cyclodecenyl, whereby the linkage can be carried out both to the double bond and to the single bonds.

[0029] As used herein, the term "halogen" is defined in each case as fluorine, chlorine, bromine or iodine, with fluorine being preferred for compounds of formula (I) and chlorine and bromine being preferred as substituent M in compounds of formula (II).

[0030] As used herein, the term "halo-C₁-C₆-alkyl" is defined as a C₁-C₆ alkyl group wherein some or all hydrogen atoms are replaced by halogen atoms, preferably replaced with fluoro atoms. Preferred is the group CF₃.

[0031] As used herein, the term "alkenyl" is defined in each case as a straight-chain or branched alkenyl radical that

contains 2-6, preferably 2-4 carbon atoms. For example, the following radicals can be mentioned: vinyl, propen-1-yl, propen-2-yl, but-1-en-1-yl, but-1-en-2-yl, but-2-en-1-yl, but-2-en-2-yl, 2-methyl-prop-2-en-1-yl, 2-methyl-prop-1-en-1-yl, but-1-en-3-yl, but-3-en-1-yl, and allyl.

[0032] As used herein, the term "aryl" is defined in each case has 6-12 carbon atoms, such as, for example, cyclopropenyl, cyclopentadienyl, phenyl, troyl, cyclooctadienyl, indenyl, naphthyl, azulenyl, biphenyl, fluorenyl, anthracenyl etc, phenyl being preferred.

[0033] As used herein, the term "heteroaryl" is defined in each case comprises 3-16 ring atoms, and instead of the carbon can contain one or more heteroatoms that are the same or different, such as oxygen, nitrogen or sulfur, in the ring, and can be monocyclic, bicyclic, or tricyclic, and in addition in each case can be benzocondensed. Preferably heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, etc., and benzo derivatives thereof, such as, e.g., benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, etc.; or pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc., and benzo derivatives thereof, such as, e.g., quinolinyl, isoquinolinyl, etc.; or azocinyl, indoliziny, purinyl, etc., and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, etc. More preferably the heteroaryl is selected from quinolinyl, isoquinolinyl, or indazolyl. Most preferably the heteroaryl is indazolyl.

[0034] As used herein, the term "C₁-C₃-dialkyl ketal" is formed when two C₁-C₃-alkoxy radicals are bonded to the same carbon atom. Preferably the C₁-C₃-alkoxy radical is -OCH₃.

[0035] As used herein, the term "C₁-C₃-cyclic ketal" is defined as a 5-6 membered ring formed when a C₁-C₃-dioxyalkyl radical such as ethan-1,2-dioxy or propan-1,3-dioxy is bonded via the oxygen atoms to the same carbon atom. Examples of C₁-C₃-cyclic ketals are 1,3-dioxolane or 1,3-dioxane rings. Preferably, C₁-C₃-cyclic ketal is -O(CH₂)₂O- such that a 1,3-dioxolane ring is formed.

[0036] The aryl radical and the heteroaryl radical in each case can be substituted in the same way or differently in one or more places with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸. It is understood that the substitution on the aryl radical and the heteroaryl radical may take place on any one of the radical's carbon atoms and/or on any one of the heteroatoms. Preferably the aryl radical and the heteroaryl radical is substituted in one or two places.

[0037] If an acid group is included, the physiologically compatible salts of organic and inorganic bases are suitable as salts, such as, for example, the readily soluble alkali salts and alkaline-earth salts as well as N-methyl-glucamine, dimethyl-glucamine, ethylglucamine, lysine, 1,6-hexdiamine, ethanolamine, glucosamine, sarcosine, serinol, trishydroxy-methyl-amino-methane, aminopropanediol, Sovak base, and 1-amino-2,3,4-butanetriol.

[0038] If a basic group is included, the physiologically compatible salts of organic and inorganic acids are suitable, such as hydrochloric acid, sulfuric acid, phosphoric acid, citric acid, tartaric acid, succinic acid, fumaric acid.

[0039] The compounds of general formula (I) according to the invention also contain the possible tautomeric forms and comprise the E-isomers or Z-isomers, or, if one or more stereogenic centers are present, racemates and/or enantiomers and/or diastereoisomers. Thus, a molecule with a single stereogenic center may be a mixture of enantiomers (*R,S*), or may be a single (*R*) or (*S*) enantiomer. A molecule with more than one stereogenic center may be a mixture of diastereoisomers, or may be a single diastereoisomer, whereby the diastereoisomers may also exist as mixtures of enantiomers or single enantiomers.

[0040] One embodiment of the present invention are compounds of formula (I) wherein X is CH.

[0041] In one embodiment, W is hydrogen.

[0042] In one embodiment, A, E, and Q are each CH.

[0043] In one embodiment, X is CH, W is hydrogen, and A, E, and Q each are CH.

[0044] In one embodiment, R¹ is aryl or heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸. In another embodiment, R¹ is heteroaryl optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸. In a preferred embodiment, R¹ is heteroaryl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸. In a more preferred embodiment, R¹ is quinolinyl, isoquinolinyl, or indazolyl which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸. In an even more preferred embodiment, R¹ is quinolinyl, isoquinolinyl, or indazolyl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸. In a most

preferred embodiment, R¹ is indazolyl substituted with C₁-C₁₂-alkyl, particularly 2-methyl-indazolyl and 1-methyl indazolyl.

[0045] In one embodiment, R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which contains no or one further heteroatom, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵.

[0046] In one embodiment, R⁴ is C₁-C₁₂-alkyl. In a preferred embodiment, R⁴ is -CH₃.

[0047] In one embodiment, R⁵ is -CH₃ or hydrogen. In a preferred embodiment, R⁵ is hydrogen.

[0048] In one embodiment, R⁶ is C₁-C₁₂-alkyl or -NR⁷R⁸. In a preferred embodiment, R⁶ is C₁-C₁₂-alkyl. In a more preferred embodiment, R⁶ is -CH₃.

[0049] In one embodiment, R⁷ and R⁸ independently of one another, are hydrogen, COR⁶, SO₂R⁶, C₁-C₁₂-alkyl. In a preferred embodiment, R⁷ and R⁸ independently of one another are hydrogen or -CH₃.

[0050] In one embodiment:

X is CH,

W is hydrogen,

A, E and Q each are CH,

R¹ is aryl or heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸,

R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-Cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵,

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl,

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl,

R⁶ hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl, or -NR⁷R⁸,

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl, or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶, and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

[0051] In a preferred embodiment:

X is CH,

W is hydrogen,

A, E and Q each are CH,

R¹ is heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸,

R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl,

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl,

R⁶ hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl, or -NR⁷R⁸,

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl, or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy,

halo-C₁-C₆-alkyl, =O, -OR⁵, COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶, and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

[0052] In a further preferred embodiment:

5 X is CH,
 W is hydrogen,
 A, E and Q each are CH,
 R¹ is quinolinyl, isoquinolinyl, or indazolyl which may be optionally substituted in one or more places in the
 10 same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸,
 R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain
 15 further heteroatoms, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;
 R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl,
 R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl,
 20 R⁶ hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl, or -NR⁷R⁸,
 R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl, or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂,
 25 or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶, and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

[0053] In a more preferred embodiment:

30 X is CH,
 W is hydrogen,
 A, E and Q each are CH,
 R¹ is quinolinyl, isoquinolinyl, or indazolyl which is substituted in one or more places in the same way or
 35 differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸,
 R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and which may be optionally substituted
 40 in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;
 R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl,
 R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl,
 R⁶ hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl, or -NR⁷R⁸,
 45 R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl, or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂,
 or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and may be optionally substituted
 50 in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶, and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

[0054] In an even more preferred embodiment:

55 X is CH,
 W is hydrogen,
 A, E and Q each are CH,
 R¹ is indazolyl which may be optionally substituted in one or more places in the same way or differently with

halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸, together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl,

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl,

R⁶ hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl, or -NR⁷R⁸,

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl, or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶, and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

[0055] In a most preferred embodiment:

X is CH,

W is hydrogen,

A, E and Q each are CH,

R¹ is indazolyl substituted with C₁-C₁₂-alkyl,

R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which may optionally contain further heteroatoms, such as nitrogen, oxygen or sulfur, and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl,

R⁵ is hydrogen,

R⁶ is C₁-C₁₂-alkyl, and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

[0056] Some specific examples of compounds of the present invention include the following:

4-hydroxy-4-methyl-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-hydroxy-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-hydroxy-4-trifluoromethyl-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

1-oxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

1,1-dioxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-methyl-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-methyl-piperazine-1-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-me-

thyl }-pyridin-2-yl)-amide,

4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-methanesulfonyl-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(7-methoxy-isoquinolin-3-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

2,6-dimethyl-morpholine-4-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

2,6-dimethyl-morpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

3-hydroxy-pyrrolidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[3-fluoro-2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(isoquinolin-3-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(3,6-difluoro-quinolin-2-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide, and

morpholine-4-carboxylic acid (4-[[2-(3-fluoro-6-methoxy-quinolin-2-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide

[0057] The compounds of formula (I) can be used as pharmaceutical agents based on their inhibitory activity relative to the phosphorylation of VEGF receptors. Based on their profile of action, the compounds according to the invention are suitable for treating diseases that are caused or promoted by persistent angiogenesis.

[0058] Since the compounds of formula (I) are identified as inhibitors of the tyrosine kinases VEGFR-1 and VEGFR-2, they are suitable in particular for treating those diseases that are caused or promoted by persistent angiogenesis that is triggered via the VEGF receptor or by an increase in vascular permeability.

[0059] The present also provides the use of the compounds of formula (I) as inhibitors of the tyrosine kinases VEGFR-1 and VEGFR-2, or KDR and FLT.

[0060] The term "diseases that are caused or promoted by persistent angiogenesis" relates especially to diseases such as tumor or metastasis growth, psoriasis, Kaposi's sarcoma, restenosis, such as, e.g., stent-induced restenosis, endometriosis, Crohn's disease, Hodgkin's disease, leukemia; arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma; eye diseases, such as diabetic retinopathy, neovascular glaucoma; corneal transplants; renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents, as immunosuppressive agents, for supporting scar-free healing, in senile keratosis, in contact dermatitis, and in asthma.

[0061] In treating injuries to nerve tissue, quick scar formation on the injury sites can be prevented with the compounds according to the invention, i.e., scar formation is prevented from occurring before the axons reconnect. A reconstruction of the nerve compounds was thus facilitated.

[0062] The formation of ascites in patients, especially patients suffering from tumors caused by metastases, can also

be suppressed with the compounds according to the invention.

VEGF-induced edemas can also be suppressed.

[0063] By a treatment with the compounds of formula (I), not only a reduction of the size of metastases but also a reduction of the number of metastases is achieved.

[0064] Lymphangiogenesis plays an important role in lymphogenic metastasis (Karpanen, T. et al., Cancer Res. **2001** Mar 1, 61(5): 1786-90, Veikkola, T., et al., EMBO J. **2001**, Mar 15; 20 (6): 1223-31).

[0065] The compounds of formula (I) also show excellent action as VEGFR kinase 3 inhibitors and are, therefore, also suitable as effective inhibitors of lymphangiogenesis.

[0066] The compounds of formula (I) are thus effective in the treatment of diseases that are associated with excessive lymphangiogenesis, such as lymphedema, lymphangiectasia, lymphangioma, and lymphangiosarcoma but also asthma. Lymphatic growth around tumors may facilitate metastatic spread of malignant cells that ultimately kill the patient. This process can be effectively hindered by the compounds of this invention. Thus the compounds are not only effective in inhibiting metastasis growth, but are also effective in reducing the number of metastases.

[0067] This invention also provides the use of the compounds of formula (I) as inhibitors of the tyrosine kinase VEGFR-3 (FLT-4).

[0068] A further object of this invention is also a pharmaceutical agent for treating diseases that are associated with excessive lymphangiogenesis, such as metastasis growth, lymphedema, lymphangiectasia, lymphangioma, and lymphangiosarcoma but also asthma.

[0069] Furthermore, the invention relates to the use of the compounds of general formula (I) for the preparation of a pharmaceutical agent for use in or for the treatment of tumor or metastasis growth, psoriasis, Kaposi's sarcoma, restenosis, such as, e.g., stent-induced restenosis, endometriosis, Crohn's disease, Hodgkin's disease, leukemia; arthritis, such as rheumatoid arthritis, hemangioma, angiofibroma; eye diseases, such as diabetic retinopathy, neovascular glaucoma; corneal transplants; renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver, mesangial cell proliferative diseases, arteriosclerosis, injuries to nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment, in vascular prosthetics or after mechanical devices are used to keep vessels open, such as, e.g., stents, as immunosuppressive agents, for supporting scar-free healing, in senile keratosis, in contact dermatitis, and also in asthma.

[0070] To use the compounds of formula (I) as pharmaceutical agents, the latter are brought into the form of a pharmaceutical preparation, which in addition to the active ingredient for enteral or parenteral administration contains suitable pharmaceutical, organic or inorganic inert carrier materials, such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. The pharmaceutical preparations can be present in solid form, for example as tablets, coated tablets, suppositories, capsules or in liquid form, for example as solutions, suspensions or emulsions. They also can contain, moreover, adjuvants such as preservatives, stabilizers, wetting agents or emulsifiers, salts for changing osmotic pressure or buffers.

[0071] For parenteral administration, especially injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxyethoxylated castor oil, are suitable.

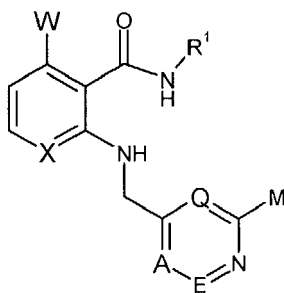
[0072] As carrier systems, surface-active adjuvants such as salts of bile acids or animal or plant phospholipids, but also mixtures thereof as well as liposomes or components thereof can also be used.

[0073] For oral administration, especially tablets, coated tablets or capsules with talc and/or hydrocarbon vehicles or binders, such as for example, lactose, corn starch or potato starch, are suitable. The administration can also be carried out in liquid form, such as, for example, as juice, to which optionally a sweetener or, if necessary, one or more flavoring substances, is added.

[0074] The dosage of the active ingredients can vary depending on the method of administration, age and weight of the patient, type and severity of the disease to be treated and similar factors. The daily dose is 0.5-1000 mg, preferably 50-200 mg, whereby the dose can be given as a single dose to be administered once or divided into 2 or more daily doses.

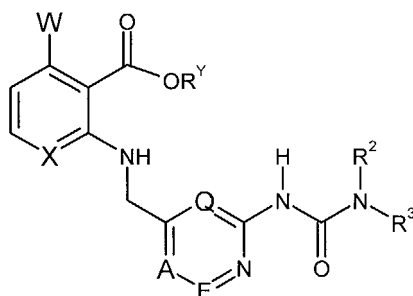
[0075] A further object of this invention is therefore a pharmaceutical agent comprising a compound of formula (I) in combination with at least one pharmaceutically acceptable carrier or excipient.

[0076] Compounds of formula (I) are obtained, in that a compound of general formula (II)



(II),

in which A, E, Q, W, X and R¹ are defined as for general formula (I) and M stands for halogen, is (i) first converted to an amine and then, by reaction with a carbamoyl chloride of formula ClCONR²R³ in which R² and R³ are defined as for general formula (I), is converted to a urea of general formula (I), or (ii) reacted with a urea of general formula H₂NCONR²R³ in which R² and R³ are defined as for general formula (I), or (iii) first converted to an amine, then converted to a compound of formula (I) by first reacting with a compound of formula ClCO₂Ph and then reacting with a compound of formula HNR²R³, wherein R² and R³ are defined as for general formula (I); or a compound of general formula (III) in which A, E, Q, W, X, R², and R³ are defined as for general formula (I) and R^Y stands for H or C₁-C₆-alkyl, is reacted with an amine of general formula R¹NH₂ in which R¹ is defined as for general formula (I),



(III)

There are many methods known in the literature for amide formation. For example, it is possible to start from the corresponding ester. The ester may be reacted according to J. Org. Chem. 1995, 8414 with trimethylaluminum and the corresponding amine in solvents such as toluene or 1,2-dichloroethane, at temperatures of 0°C to the boiling point of the solvent. If the molecule contains two ester groups, both are converted into the same amide. Instead of trimethylaluminum, sodium hexamethyldisilazide can also be used.

[0077] For amide formation, however, all processes that are known from peptide chemistry are also available. For example, the corresponding acid, obtained from the corresponding ester by saponification, can be reacted with the amine in aprotic polar solvents, such as, for example, dimethylformamide, via an activated acid derivative, obtainable, for example, with hydroxybenzotriazole and a carbodiimide, such as, for example, diisopropylcarbodiimide, at temperatures of between 0°C and the boiling point of the solvent, preferably at 80°C, or else with preformed reagents, such as, for example, HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (Chem. Comm. **1994**, 201), at temperatures of between 0°C and the boiling point of the solvent, preferably at room temperature. The addition of a base such as N-methylmorpholine, for example, is necessary. Amide formation, may also be accomplished via the acid halide, mixed acid anhydride, imidazolide or azide. The ureas of aryl- or heteroaryl amines may be prepared by a variety of literature known methods. For example, they may be prepared by the reaction of aryl- or heteroaryl amines with isocyanates, the reaction of amines with aryl- or heteroaryl-carbamates such as aryl- or heteroaryl-phenoxy-carbamates, or the reaction of aryl- or heteroaryl amines with appropriately substituted carbamoyl chlorides, or the reaction of an aryl- or heteroaryl-halide with ureas under the influence of metal catalysis.

[0078] For example, the ureas of aminopyridines may be prepared by reacting a urea with halopyridines, whereby chloro and bromopyridines are preferred, under the catalytic influence of metal complexes, for example, palladium- or copper complexes. In the case of copper complexes the use of stoichiometric amounts of the copper complexes may be advantageous for the reaction outcome. Suitable copper salts for the reaction are copper (I) or copper (II) salts whereby copper (I) salts such as, for example, copper (I) oxide or copper (I) iodide, are preferred. In the case of copper (I) iodide the addition of an additive such as, for example, ethylenediamine is necessary. Suitable solvents for this copper promoted coupling are dioxane or dimethylformamide, at temperatures upto the boiling point of the solvents, whereby 120 °C is preferred. Addition of a base is also necessary, such as potassium phosphate or cesium carbonate. In the case of palladium catalysis, palladium complexes such as tris-(dibenzylideneacetone) -dipalladium(0) maybe employed. Suitable solvents for the reaction are toluene, dioxane or dimethylformamide, whereby mixtures of solvents may also be advantageous for the reaction, at temperatures from room temperature to the boiling points of the solvents, whereby 110°C is preferred. A co-ligand such as BINAP, DPPF or xantphos is also employed. A base is also required, suitable bases for the reaction are for example, cesium carbonate, potassium phosphate or sodiumtertbutoxide.

[0079] The required urea starting materials for the above copper or palladium promoted coupling, may in turn be prepared from the reaction of the corresponding amines with the corresponding isocyanates. Solvents such as for example dichloromethane, or isopropylalcohol may be employed at temperatures from 0°C to the boiling points of the solvents, whereby room temperature is preferred.

[0080] Methods for the preparation of substituted or unsubstituted 6-aminoindazoles are well known in the literature. They may be obtained from the reduction of the corresponding nitroindazoles via catalytic hydrogenation or other well known reduction methods. N-alkylation of substituted nitroindazoles may be accomplished with a variety of literature known alkylating agents. For example, methylation of N-1 or N-2 of a suitably functionalised 6-nitroindazole may be accomplished by for example treatment with a base, preferably Cs_2CO_3 or NaH, and a methyl halide, preferably methyl iodide in a suitable solvent such as N,N-dimethylformamide, at temperatures ranging from 0 °C to 50 °C, whereby 50 °C is preferred. 3-Substituted-6-nitroindazoles may be prepared by a variety of methods. For example alkyl substituents may be introduced in the 3-position by way of standard Suzuki reactions between an appropriate 3-haloindazole, whereby the appropriate 3-iodoindazoles are preferred, and an alkyl boronic acid, whereby the trialkylboroxines may also be employed. N-protection of the indazole may be advantageous for the reaction. 6-Nitroindazole-3-carboxylic acid provides a suitable starting material for ester, amide, hydroxymethyl and alkoxymethyl substitution in the 3-position of 6-nitroindazole, via well known transformations such as transesterification, amide coupling, reduction, or reduction followed by alkylation. 6-Nitroindazole-3-carbaldehyde (prepared by the reaction of commercial 6-nitroindole with NaNO_2 in the presence of dilute aqueous hydrochloric acid according to J. Med. Chem. **2001**, 44, 7, 1021) provides a useful precursor to 6-nitroindazole-3-carboxylic acid via well known oxidation methods. In turn 6-nitroindazole-3-carbaldehyde may also be converted to 3-hydroxymethyl-6-nitroindazole, 3-alkoxymethyl-6-nitroindazole, or 3-aminomethyl-6-nitroindazole derivatives by equally standard transformations such as reduction, reduction followed by alkylation, or reductive amination. Such standard transformations may also be applied to the synthesis of other substituted aminoindazoles. A variety of substituted nitroindazoles are commercially available, however they may be readily synthesised via the reaction of a suitable 2-amino-nitrotoluene derivative with, for example, NaNO_2 and aqueous hydrochloric acid. If required, the nitro group may be introduced after the cyclisation reaction of a suitable 2-aminotoluene derivative by standard nitration chemistry.

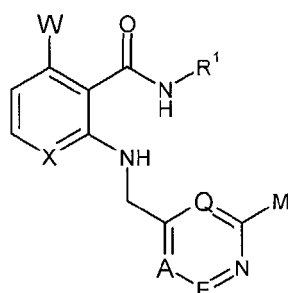
[0081] The preparation of N-alkylated-aminobenzimidazoles may be accomplished from the corresponding N-alkylated-nitrobenzimidazoles via standard reduction chemistry. Alkylation of a suitable functionalised nitrobenzimidazole, for example with an alkyl halide and a base, furnishes N1- and N3-alkylated-nitrobenzimidazoles, which may be separated and isolated in pure form by standard purification techniques. For example, 6-amino-1-methyl-benzimidazole may be produced by the reaction of commercial 5-nitrobenzimidazole with MeI and Cs_2CO_3 in DMF followed by purification (of the resulting mixture of 5- and 6-nitro-1-methyl-benzimidazoles) and hydrogenation in the presence of 10% Pd on charcoal. Similarly, the preparation of N-alkylatedaminobenzotriazoles may also be accomplished from the corresponding nitrobenzotriazoles. Alkylation of a suitable functionalised nitrobenzotriazole, for example with an alkyl halide and a base, furnishes N1-, N2- and N3-alkylatednitrobenzotriazoles, which may be separated and isolated in pure form by standard purification techniques. Standard reduction chemistry furnishes the corresponding aminobenzotriazoles. For example, 5-amino-2-methyl-benzotriazole may be prepared according to a literature procedure (Eur. J. Med. Chem. **1992**, 27, 161-166).

[0082] The preparation of 3-aminoisoquinolines which are substituted in the 7-position, may be accomplished via the corresponding 3-amino-1-bromo-7-substituted isoquinoline by way of reductive dehalogenation. 3-amino-1-bromo-7-substituted isoquinolines may in turn be prepared by the reaction of a suitable 2-cyano-4-substituted-benzeneacetonitrile with HBr in acetic acid. For example, 3-amino-7-methoxyisoquinoline may be prepared in two steps (HBr mediated cyclisation followed by reductive dehalogenation) from 2-cyano-4-methoxy-benzeneacetonitrile, which may be prepared according to a literature procedure (Bull. Chem. Soc. Jpn. **1980**, 53, 10, 2885-2890).

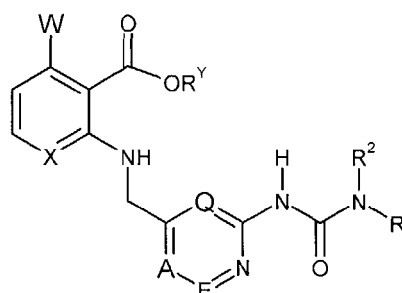
[0083] 1-Alkyl-6-amino-quinolin-2-ones may be prepared by known methods. For example, 6-amino-2-methyl-quinolin-

2-one may be prepared according to a literature procedure (J. Chem. Research, Synopses, **1997**, 310-311). 2-Amino-3,6-disubstituted quinolines may be prepared by a number of procedures. For example, the reaction of the lithium salt (generated with a base such as lithium diisopropylamide) of a suitably substituted cyanomethyl-dialkylphosphonate with a suitably substituted 2-nitrobenzaldehyde derivative in a suitable solvent, such as THF, furnishes a suitable acrylonitrile derivative which may be cyclised to the desired 2-amino-3,6-disubstituted quinoline by treating with a suitable reducing agent, such as iron in acetic acid.

[0084] The compounds of the general formulae II and III



(II),



(III),

in which A, E, Q, W, R¹, R² and R³, are defined in the same way as for the general formula (I), M is halogen and Rʸ is H or C₁-C₆-alkyl, provide valuable intermediates for the preparation of the inventive compounds of general formula (I) and, are therefore also objects of the invention. The use of compounds of formula (II) and (III) in the production of a compound of formula (I), as well as the process described above using these compounds in the production of a compound of formula (I) are also objects of the invention.

Production of the compounds according to the invention

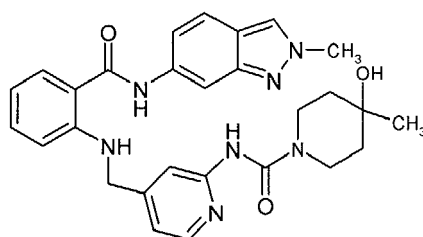
[0085] The following examples explain the production of the compounds according to the invention without the scope of the claimed compounds being limited to these examples.

Abbreviations

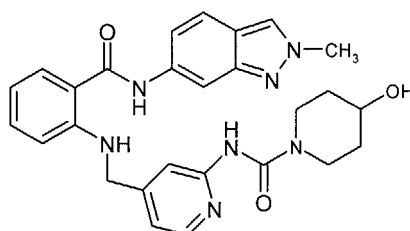
[0086] The following abbreviations used in the invention have the following meanings:

Brine	saturated aqueous sodium chloride solution
CI+	chemical ionisation (NH₃)
DCE	1,2-dichloroethane
DMF	N,N-dimethyl formamide
d₆-DMSO	d₆-dimethylsulfoxide
d	doublet
dd	doublet of doublets
ES+	positive mode electrospray ionisation
EtOAc	ethyl acetate
EtOH	ethanol
¹H-NMR	proton nuclear magnetic resonance spectroscopy
Hex	n-hexane
LC-ES+	liquid chromatography / positive mode electrospray ionisation
LDA	Lithium diisopropylamide
MeOH	methanol
m	multiplet
Mp.	melting point
MS	mass spectrometry
m/z	mass / charge ratio
Pd₂dba₃	tris-(dibenzylideneacetone)-dipalladium(0)-chloroform complex

rt	room temperature
RT	retention time (LC)
s	singlet
THF	tetrahydrofuran
t	triplet
Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

Example 1.0**Preparation of 4-hydroxy-4-methyl-piperidine-1-carboxylic acid (4-([2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl)-pyridin-2-yl)-amide****[0087]**

4-oxo-piperidine-1-carboxylic acid (4-([2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl)-pyridin-2-yl)-amide (50 mg, 0.1 mmol) in dry THF under argon, at -78 °C was treated dropwise with methyllithium (1.5M in diethylether, 0.2 mL, 0.3 mmol). The reaction was stirred for 30 minutes at -78 °C before warming to rt. The reaction was stirred overnight before partitioning between EtOAc and saturated aqueous ammonium chloride solution. The organic phase was washed with brine, dried, filtered and concentrated in vacuo. The residue was purified by chromatography on Isolute® Flash silica gel (Separtis) (Gradient elution: 100% CH₂Cl₂ to CH₂Cl₂/EtOH 10:2) to give 4-hydroxy-4-methyl-piperidine-1-carboxylic acid (4-([2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl)-pyridin-2-yl)-amide (12 mg, 23%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.13 (1H, s), 9.02 (1H, s), 8.25 (1H, s), 8.13 (1H, d), 8.10 (1H, s), 7.94 (1H, t), 7.80 (1H, s), 7.72 (1H, d), 7.64 (1H, d), 7.23-7.32 (2H, m), 6.92 (1H, d), 6.66 (1H, t), 6.54 (1H, d), 4.43 (2H, d), 4.31 (1H, s), 4.13 (3H, s), 3.68-3.74 (2H, m), 3.16-3.25 (2H, m), 1.35-1.46 (4H, m), 1.12 (3H, s); m/z (ES⁺) 514 [M+H]⁺.

Example 1.1**Preparation of 4-hydroxy-piperidine-1-carboxylic acid (4-([2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl)-pyridin-2-yl)-amide****[0088]**

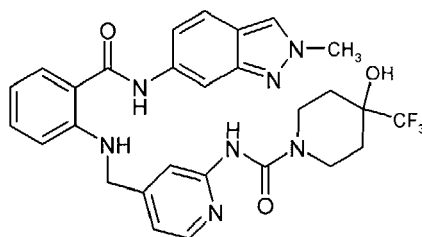
4-oxo-piperidine-1-carboxylic acid (4-([2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl)-pyridin-2-yl)-amide (50 mg, 0.1 mmol) in absolute EtOH, at 4 °C was treated with sodium borohydride (4 mg, 0.1 mmol). The reaction was warmed to rt and stirred for 1 hour before the reaction was partitioned between EtOAc and water. The

organic phase was washed with brine, dried, filtered and concentrated in vacuo to give 4-hydroxy-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (39 mg, 78%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1 H, s), 9.07 (1H, s), 8.26 (1H, s), 8.14 (1 H, d), 8.10 (1 H, s), 7.94 (1H, t), 7.79 (1H, s), 7.71-7.73 (1H, m), 7.64 (1H, d), 7.30-7.33 (1H, m), 7.23-7.28 (1H, m), 6.92-6.94 (1H, m), 6.66 (1H, t), 6.54 (1H, d), 4.68 (1H, d), 4.43 (2H, d), 4.13 (3H, s), 3.79-3.84 (2H, m), 3.60-3.67 (1H, m), 3.00-3.08 (2H, m), 1.70-1.73 (2H, m), 1.23-1.35 (2H, m); m/z (ES+) 500 [M+H]⁺.

Example 1.2

Preparation of 4-hydroxy-4-trifluoromethyl-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide

[0089]

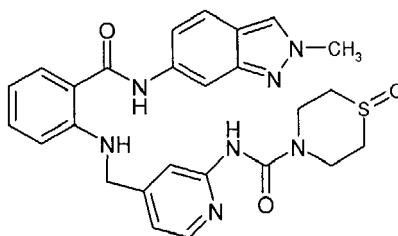


4-oxo-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (140 mg, 0.28 mmol) in dry THF was treated successively with trifluoromethyltrimethylsilane (0.06 mL, 0.42 mmol) and tetra-n-butylammonium fluoride (1M solution in THF, 0.28 mL, 0.28 mmol). The reaction was stirred at rt overnight before it was partitioned between EtOAc and water. The organic phase was washed with brine, dried, filtered and concentrated in vacuo. The residue was purified by chromatography on Isolute® Flash silica gel (Separtis) (Gradient elution: 100% CH₂Cl₂ to CH₂Cl₂/EtOH 10:1) to give 4-hydroxy-4-trifluoromethyl-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (15 mg, 9%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1H, s), 9.21 (1H, s), 8.25 (1H, s), 8.15 (1H, d), 8.10 (1H, s), 7.95 (1H, t), 7.80 (1H, s), 7.72 (1H, d), 7.63 (1H, d), 7.23-7.32 (2H, m), 6.94 (1H, d), 6.66 (1H, t), 6.53 (1H, d), 6.02 (1H, s), 4.44 (2H, d), 4.07-4.17 (5H, m), 2.95-3.05 (2H, m), 1.55-1.63 (4H, m); m/z (ES+) 568 [M+H]⁺.

Example 2.0

Preparation of 1-oxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide

[0090]



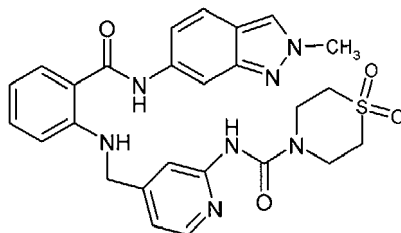
A mixture of thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (50 mg, 0.1 mmol) and sodium periodate (43 mg, 0.2 mmol) in MeOH/water (3:1, 4 mL) was stirred overnight at rt. The reaction was partitioned between EtOAc and brine and the organic phase dried, filtered and concentrated in vacuo to give 1-oxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-me-

thyl)-pyridin-2-yl)-amide (30 mg, 58%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1H, s), 9.37 (1H, s), 8.25 (1H, s), 8.17 (1H, d), 8.10 (1H, s), 7.96 (1H, t), 7.82 (1H, s), 7.71-7.74 (1H, m), 7.63 (1H, d), 7.23-7.32 (2H, m), 6.96-6.98 (1H, m), 6.67 (1H, t), 6.54 (1H, d), 4.45 (2H, d), 4.13 (3H, s), 3.99-4.04 (2H, m), 3.66-3.74 (2H, m), 2.84-2.93 (2H, m), 2.65-2.70 (2H, m); m/z (LC-ES+) 518 [M+H]⁺.

Example 2.1

Preparation of 1,1-dioxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide

[0091]

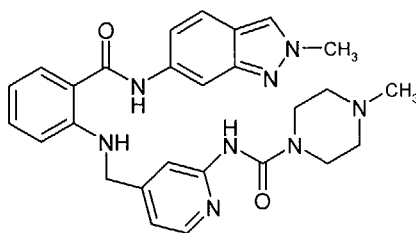


Thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (89 mg, 0.18 mmol) in acetone (6 mL) and distilled water (1.5 mL) was treated successively with 4-methylmorpholine-N-oxide (63 mg, 0.54 mmol) and osmiumtetroxide (2.5% solution in water, 0.01 mL, catalytic). The reaction was stirred overnight before quenching with saturated aqueous sodium bisulfite solution. The mixture was extracted with CH₂Cl₂ and the organic phase was washed with water, dried, filtered and concentrated in vacuo to give 1,1-dioxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (44 mg, 46%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1H, s), 9.53 (1H, s), 8.25 (1H, s), 8.17 (1H, d), 8.10 (1H, s), 7.96 (1H, t), 7.81 (1H, s), 7.71-7.73 (1H, m), 7.63 (1H, d), 7.23-7.32 (2H, m), 6.97-6.99 (1H, m), 6.67 (1H, t), 6.54 (1H, d), 4.45 (2H, d), 4.13 (3H, s), 3.87-3.90 (4H, m), 3.15-3.17 (4H, m); m/z (ES+) 534 [M+H]⁺.

Example 3.0

Preparation of 4-methyl-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide

[0092]

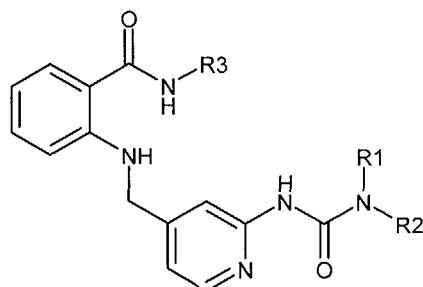


2-[[2-bromo-pyridin-4-ylmethyl]-amino]-N-(2-methyl-2H-indazol-6-yl)-benzamide (110 mg, 0.25 mmol) was suspended in dioxane (3 mL) and treated consecutively with DMF (1 mL), Pd₂dba₃ (5 mg, 0.005 mmol), Xantphos (9 mg, 0.015 mmol), cesium carbonate (98 mg, 0.3 mmol) and 4-methyl-piperazine-1-carboxylic acid amide (184 mg, 1.3 mmol). The reaction mixture was placed under a nitrogen atmosphere and heated for 3 hours at 110°C (bath temperature). On cooling the volatiles were removed in vacuo and the residue was partitioned between CH₂Cl₂ and water. The organic phase was washed with brine, dried, filtered and concentrated. The residue was purified by chromatography using Isolute® Flash NH₂ (Separtis) as stationary phase (Gradient elution: 100% CH₂Cl₂ to CH₂Cl₂/EtOH 95:5) to give 4-methyl-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide.

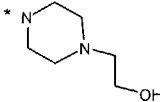
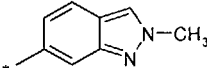
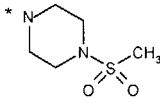
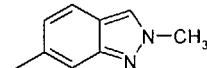
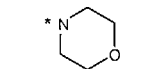
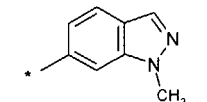
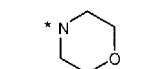
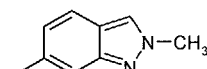
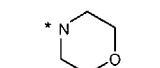
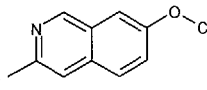
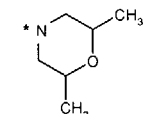
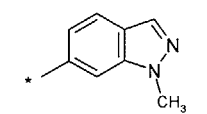
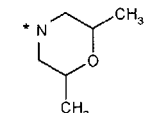
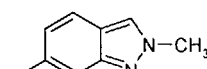
EP 1 657 241 A1

yl)-amide (28 mg, 22%) as a foam; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1H, s), 9.11 (1H, s), 8.25 (1H, s), 8.14 (1H, d), 8.10 (1 H, s), 7.95 (1H, t), 7.80 (1H, s), 7.72 (1H, d), 7.63 (1H, d), 7.23-7.32 (2H, m), 6.94 (1H, d), 6.66 (1H, t), 6.53 (1H, d), 4.43 (2H, d), 4.13 (3H, s), 3.41-3.44 (4H, m), 2.25-2.28 (4H, m), 2.17 (3H, s); m/z (ES+) 499.

[0093] The following compounds were prepared in analogy from the corresponding 2-bromopyridine intermediate and the corresponding urea intermediate:



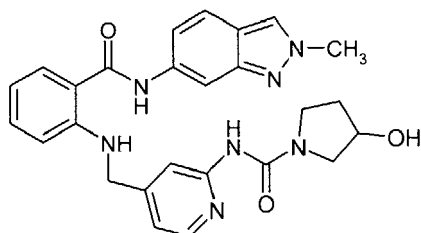
Example Nr.		R ³	MW	Mp. [°C] or MS (m/z)
3.1			498.59	Foam (ES+) 499 [M+H] ⁺
3.2			528.61	Foam (ES+) 529 [M+H] ⁺

3.3			528.61	Foam (ES+) 529 [M+H] ⁺
3.4			562.65	Foam (ES+) 563 [M+H] ⁺
3.5			485.54	Foam (ES+) 486 [M+H] ⁺
3.6			485.54	Foam (ES+) 486 [M+H] ⁺
3.7			512.57	Mp. 271
3.8			513.60	Foam (ES+) 514 [M+H] ⁺
3.9			513.60	Foam (ES+) 514 [M+H] ⁺

Example 4.0

Preparation of 3-hydroxy-pyrrolidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-yl)carbamoyl]-phenylamino]-methyl]-pyridin-2-yl)-amide

[0094]



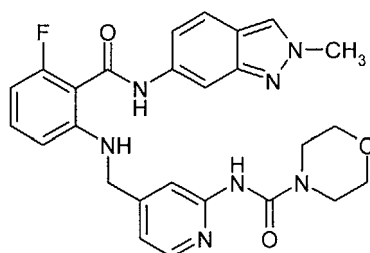
2-[[2-(2-bromo-pyridin-4-ylmethyl)-amino]-N-(2-methyl-2H-indazol-6-yl)-benzamide (400 mg, 0.92 mmol) was suspended in dioxane (15 mL) and treated consecutively with DMF (5 mL), Pd₂dba₃ (19 mg, 0.02 mmol), Xantphos (32 mg, 0.06

mmol), cesium carbonate (358 mg, 1.1 mmol) and 3-hydroxy-pyrrolidine-1-carboxylic acid amide (358 mg, 2.75 mmol). The reaction mixture was placed under a nitrogen atmosphere and heated for 3 hours at 110°C (bath temperature). On cooling the reaction was partitioned between EtOAc and water. The organic phase was washed with brine, dried, filtered and concentrated in vacuo. The residue was purified by chromatography on Isolute® Flash silica gel (Separtis) (Gradient elution: 100% CH₂Cl₂ to CH₂Cl₂/EtOH 10:1) to give 3-hydroxy-pyrrolidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (270 mg, 61%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1H, s), 8.62 (1H, s), 8.25 (1H, s), 8.14 (1H, d), 8.10 (1H, s), 7.95 (1H, t), 7.90 (1H, s), 7.71-7.73 (1H, m), 7.64 (1H, d), 7.23-7.33 (2H, m), 6.93-6.95 (1H, m), 6.67 (1H, t), 6.53 (1H, d), 4.93 (1H, d), 4.43 (2H, d), 4.26 (1H, m), 4.13 (3H, s), 3.40-3.48 (4H, m), 1.79-1.94 (2H, m); m/z (ES⁺) 486 [M+H]⁺.

Example 5.0

Preparation of morpholine-4-carboxylic acid (4-[[3-fluoro-2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide

[0095]



2-[[2-Bromo-pyridin-4-ylmethyl]-amino]-6-fluoro-N-(2-methyl-2H-indazol-6-yl)-benzamide (227 mg, 0.5 mmol) was suspended in dioxane (4 mL) and treated consecutively with DMF (1.6 mL), Pd₂dba₃ (13 mg, 0.013 mmol), Xantphos (18 mg, 0.031 mmol), cesium carbonate (193 mg, 0.59 mmol) and morpholine-4-carboxylic acid amide (244 mg, 0.75 mmol). The reaction mixture was placed under an argon atmosphere and heated for 3 hours at 110°C (bath temperature). On cooling the reaction was partitioned between EtOAc and water. The organic phase was dried, filtered and concentrated in vacuo. The residue was purified by chromatography on Isolute® Flash silica gel (Separtis) (Gradient elution: 100% CH₂Cl₂ to CH₂Cl₂/EtOH 10:1) to give morpholine-4-carboxylic acid (4-[[3-fluoro-2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide (132 mg, 52%) as a pale yellow resin. Further purification was accomplished by preparative reverse phase HPLC [Column: Kromasil C8 5μ, 125x20mm. Eluant: 38% CH₃CN in H₂O (containing 0.2% NH₃) to 95% CH₃CN in H₂O (containing 0.2% NH₃)]; ¹H-NMR (300 MHz, d₆-DMSO) 10.43 (1H, s), 9.15 (1H, s), 8.26 (1H, s), 8.23 (1H, s), 8.15 (1H, d), 7.79 (1H, s), 7.64 (1H, d), 7.13-7.25 (2H, m), 6.95 (1H, d), 6.73 (1H, t), 6.48 (1H, t), 6.29 (1H, d), 4.40 (2H, d), 4.14 (3H, s), 3.56-3.59 (4H, m), 3.42-3.45 (4H, m); m/z (ES⁺) 504 [M+H]⁺.

Example 6.0

Preparation of morpholine-4-carboxylic acid (4-[[2-(isoquinolin-3-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide

[0096]



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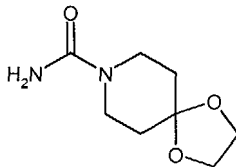
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Example 7.0**Preparation of 1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid amide**

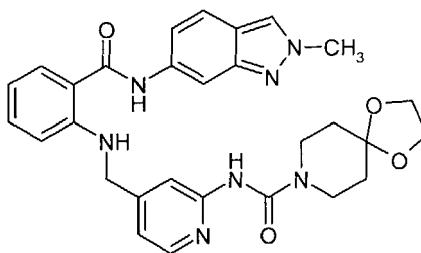
[0099]



To a stirred solution of 1,4-dioxa-8-azaspiro[4.5]decane (1.1 g, 7.67 mmol) in isopropanol (20 mL) at rt was added trimethylsilylisocyanate (1.5 mL, 10.6 mmol) and the resulting solution stirred overnight before the volatiles were removed in vacuo to give 1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid amide (1.47 g, quant.); ¹H-NMR (300 MHz, d₆-DM-SO) 5.96 (2H, s), 3.88 (4H, s), 3.33 (4H, t), 1.51 (4H, t).

Example 7.1**Preparation of 1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid (4-{{[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl}-pyridin-2-yl)-amide**

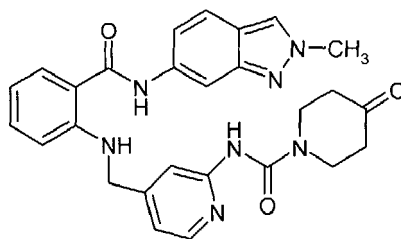
[0100]



2-[[2-bromo-pyridin-4-ylmethyl)-amino]-N-(2-methyl-2H-indazol-6-yl)-benzamide (700 mg, 1.6 mmol) was suspended in dioxane (26 mL) and treated consecutively with DMF (7 mL), Pd₂dba₃ (32 mg, 0.03 mmol), Xantphos (61mg, 0.1 mmol), cesium carbonate (632 mg, 1.9 mmol) and 1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid amide (930 mg, 5 mmol). The reaction mixture was placed under a nitrogen atmosphere and heated for 4 hours at 110°C (bath temperature). On cooling the reaction was partitioned between EtOAc and brine. The organic phase was dried, filtered and concentrated in vacuo. The residue was purified by chromatography on Isolute® Flash silica gel (Separtis) (Gradient elution: 100% CH₂Cl₂ to CH₂Cl₂/EtOH 10:1) to give 1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid(4-{{[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl}-pyridin-2-yl)-amide (574mg, 66%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.20 (1H, s), 9.25 (1H, s), 8.32 (1H, s), 8.21 (1H, d), 8.17 (1H, s), 8.01 (1H, t), 7.87 (1H, s), 7.75-7.80 (1H, m), 7.70 (1H, d), 7.30-7.40 (2H, m), 6.99-7.01 (1H, m), 6.73 (1H, t), 6.60 (1H, d), 4.50 (2H, d), 4.20 (3H, s), 3.97 (4H, s), 3.54-3.59 (4H, m), 1.53-1.58 (4H, m); m/z (ES⁺) 542 [M+H]⁺.

Example 7.2**Preparation of 4-oxo-piperidine-1-carboxylic acid (4-{{[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl}-pyridin-2-yl)-amide**

[0101]

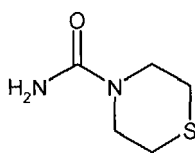


1,4-Dioxo-8-aza-spiro[4.5]decan-8-carboxylic acid(4-{{2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino}-methyl}-pyridin-2-yl)-amide (564 mg, 1.04 mmol) in acetone (35 mL), was cooled to 4 °C and treated dropwise with aqueous hydrochloric acid (4 N, 9 mL). The reaction was warmed to rt and stirred overnight. The reaction was made basic by the addition of saturated aqueous sodium hydrogencarbonate and extracted with EtOAc. The organic phase was washed with brine, dried, filtered and concentrated in vacuo to give 4-oxo-piperidine-1-carboxylic acid (4-{{2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino}-methyl}-pyridin-2-yl)-amide (467 mg, 90%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1H, s), 9.36 (1H, s), 8.25 (1H, s), 8.17 (1H, d), 8.10 (1H, s), 7.96 (1H, t), 7.86 (1H, s), 7.72 (1H, d), 7.64 (1H, d), 7.23-7.32 (2H, m), 6.96-6.98 (1H, m), 6.66 (1H, t), 6.55 (1H, d), 4.45 (2H, d), 4.13 (3H, s), 3.72-3.76 (4H, m), 2.36-2.40 (4H, m); m/z (ES⁺) 498 [M+H]⁺.

Example 8.0

Preparation of thiomorpholine-4-carboxylic acid amide

[0102]

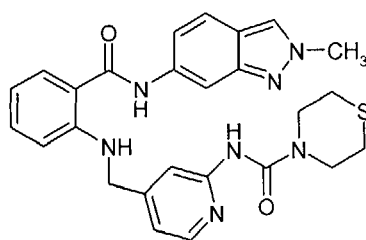


To a stirred solution of thiomorpholine (1.0 g, 9.7 mmol) in isopropanol (25 mL) at rt was added trimethylsilylisocyanate (1.9 mL, 13.45 mmol) and the resulting solution stirred overnight. The resulting suspension was filtered and the filtrate concentrated in vacuo to give thiomorpholine-4-carboxylic acid amide (1.18 g, 89%); ¹H-NMR (300 MHz, d₆-DMSO) 6.00 (2H, s), 3.53-3.57 (4H, m), 2.46-2.51 (4H, m, obscured by solvent).

Example 8.1

Preparation of thiomorpholine-4-carboxylic acid (4-{{2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino}-methyl}-pyridin-2-yl)-amide

[0103]

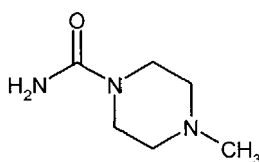


2-[(2-bromo-pyridin-4-ylmethyl)-amino]-N-(2-methyl-2H-indazol-6-yl)-benzamide (500 mg, 1.15 mmol) was suspended in dioxane (14 mL) and treated consecutively with DMF (5 mL), Pd₂dba₃ (23 mg, 0.023 mmol), Xantphos (42 mg, 0.07 mmol), cesium carbonate (454 mg, 1.38 mmol) and thiomorpholine-4-carboxylic acid amide (511 mg, 3.5 mmol). The reaction mixture was placed under a nitrogen atmosphere and heated for 4 hours at 110°C (bath temperature). On cooling the reaction was partitioned between EtOAc and water. The organic phase was washed with brine, dried, filtered and concentrated in vacuo. The residue was purified by chromatography on Isolute® Flash silica gel (Separtis) (Gradient elution: 100% CH₂Cl₂ to CH₂Cl₂/EtOH 10:1) to give thiomorpholine-4-carboxylic acid (4- {[(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl}-pyridin-2-yl)-amide (375 mg, 65%) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 10.14 (1H, s), 9.20 (1 H, s), 8.25 (1 H, s), 8.15 (1H, d), 8.11 (1H, s), 7.95 (1 H, t), 7.80 (1H, s), 7.72 (1 H, d), 7.63 (1 H, d), 7.23-7.33 (2H, m), 6.95 (1H, d), 6.67 (1H, t), 6.54 (1H, d), 4.44 (2H, d), 4.13 (3H, s), 3.70-3.73 (4H, m), 2.55-2.58 (4H, m); m/z (ES⁺) 502 [M+H]⁺.

Example 9.0

Preparation of 4-methyl-piperazine-1-carboxylic acid amide

[0104]

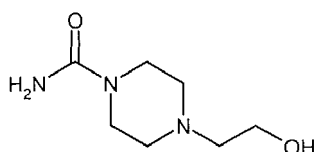


To a stirred solution of 1-methylpiperazine (1.66 mL, 15 mmol) in isopropanol (30 mL) at rt was added trimethylsilyl isocyanate (2.8 mL, 21 mmol) and the resulting solution stirred overnight. The volatiles were removed in vacuo to give 4-methyl-piperazine-1-carboxylic acid amide (2.6 g, quant.) as an oil which slowly crystallised on standing; ¹H-NMR (300 MHz, CDCl₃) 4.62 (2H, s), 3.40 (4H, t), 2.39 (4H, t), 2.29 (3H, s); m/z (ES⁺) 143 [M+H]⁺.

Example 10.0

Preparation of 4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid amide

[0105]



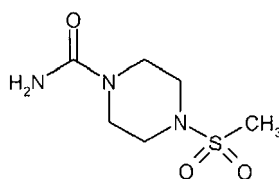
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To a stirred solution of 1-(2-hydroxy-ethyl)-piperazine (1.95 g, 15 mmol) in isopropanol (30 mL) at rt was added trimethylsilylisocyanate (2.8 mL, 21 mmol) and the resulting solution stirred overnight before the volatiles were removed in vacuo. The residue was partitioned between CH₂Cl₂ and water. The aqueous phase was concentrated in vacuo to give 4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid amide (2.3 g, 88%); ¹H-NMR (300 MHz, d₆-DMSO) 5.92 (2H, s), 4.40 (1H, t), 3.46-3.52 (2H, m), 3.22-3.34 (4H, m), 2.30-2.39 (6H, m); m/z (ES+) 173 [M+H]⁺.

Example 11.0

Preparation of 4-methanesulfonyl-piperazine-1-carboxylic acid amide

[0106]

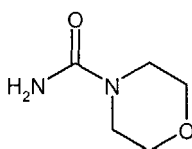


To a stirred suspension of *N*-methanesulfonylpiperazine (1.0 g, 6.1 mmol) in isopropanol (15 mL) at rt was added trimethylsilylisocyanate (1.4 mL, 11 mmol) and the resulting suspension stirred overnight before the precipitate was filtered and dried to give 4-methanesulfonyl-piperazine-1-carboxylic acid amide (1.35 g, quant.) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 6.10 (2H, s), 3.37-3.40 (4H, m), 3.03-3.06 (4H, m), 2.90 (3H, s).

Example 12.0

Preparation of morpholine-4-carboxylic acid amide

[0107]

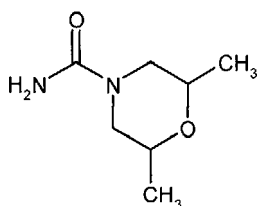


To a stirred solution of morpholine (1.3 mL, 15 mmol) in isopropanol (30 mL) at rt was added trimethylsilylisocyanate (2.8 mL, 21 mmol) and the resulting solution stirred overnight before the volatiles were removed in vacuo to give morpholine-4-carboxylic acid amide (2.0 g, quant.) as a solid; ¹H-NMR (300 MHz, d₆-DMSO) 6.00 (2H, s), 3.51-3.54 (4H, s), 3.23-3.26 (4H, s).

Example 13.0

Preparation of 2,6-dimethyl-morpholine-4-carboxylic acid amide

[0108]

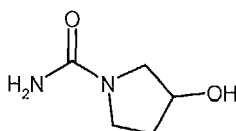


To a stirred solution of 2,6-dimethylmorpholine (mixture of cis- and trans-isomers, 1.7 g, 15 mmol) in isopropanol (30 mL) at rt was added trimethylsilylisocyanate (2.8 mL, 21 mmol) and the resulting solution stirred overnight before the volatiles were removed in vacuo to give a mixture of cis- and trans-2,6-dimethyl-morpholine-4-carboxylic acid amide (2.7 g, quant.) as a solid; m/z (ES+) 158 [M+H]⁺.

Example 14.0

Preparation of 3-hydroxy-pyrrolidine-1-carboxylic acid amide

[0109]

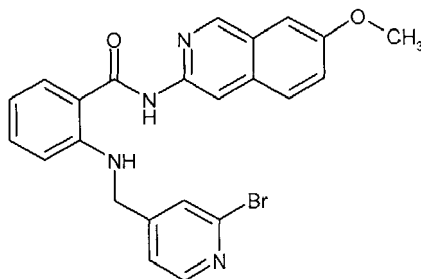


To a stirred solution of 3-hydroxypyrrolidine (1.0 g, 11.48 mmol) in isopropanol (27 mL) at rt was added trimethylsilyl-isocyanate (2.14 mL, 16.07 mmol) and the resulting solution stirred overnight. The resulting suspension was filtered and the residue washed with isopropanol and dried to give 3-hydroxy-pyrrolidine-1-carboxylic acid amide (0.89 g, 60%); ¹H-NMR (300 MHz, d₆-DMSO) 5.64 (2H, s), 4.85 (1H, d), 4.21-4.22 (1H, m), 3.22-3.28 (3H, m), 3.06-3.10 (1H, m), 1.79-1.90 (1H, m), 1.67-1.76 (1H, m).

Example 15.0

Preparation of 2-[(2-bromo-pyridin-4-ylmethyl)-amino]-N-(7-methoxy-isoquinolin-3-yl)-benzamide

[0110]



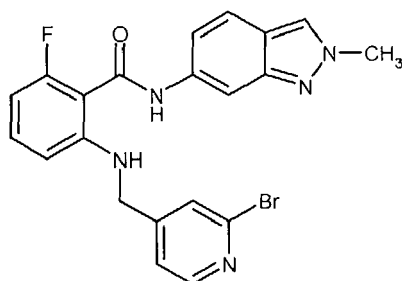
2-[(2-Bromo-pyridin-4-ylmethyl)-amino]-N-(7-methoxy-isoquinolin-3-yl)benzamide was prepared from 2-[(2-bromo-pyridin-4-ylmethyl)-amino]-benzoic acid methyl ester and 3-amino-7-methoxyisoquinoline in analogy to the procedures detailed in W02004/01302; ¹H-NMR (300 MHz, d₆-DMSO) 10.62 (1H, s), 9.10 (1H, s), 8.51 (1H, s), 8.32 (1H, d), 8.11 (1H, t), 7.83-7.90 (2H, m), 7.60 (1H, s), 7.50 (1H, m), 7.38-7.41 (2H, m), 7.27 (1H, t), 6.66 (1H, t), 6.55 (1H, d), 4.54 (2H, d),

3.91 (3H, s).

Example 16.0

Preparation of 2-[(2-bromo-pyridin-4-ylmethyl)-amino]-6-fluoro-N-(2-methyl-2H-indazol-6-yl)-benzamide

[0111]

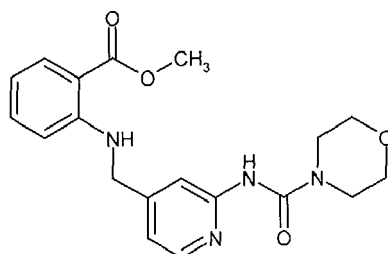


2-[(2-Bromo-pyridin-4-ylmethyl)-amino]-6-fluoro-N-(2-methyl-2H-indazol-6-yl)-benzamide was prepared from methyl 2-amino-6-fluorobenzoate via reductive amination with 2-bromo-pyridine-4-carbaldehyde, followed by subsequent amidation with 6-amino-2-methyl-indazole in analogy to the procedures detailed in W02004/01302; ¹H-NMR (300 MHz, d₆-DM-SO) 10.51 (1H, s), 8.31 (1H, d), 8.26-8.28 (2H, m), 7.65 (1H, d), 7.59 (1H, s), 7.40 (1H, d), 7.13-7.25 (2H, m), 6.73 (1H, t), 6.50 (1H, t), 6.29 (1H, d), 4.47 (2H, d), 4.13 (3H, s).

Example 17.0

Preparation of 2-({2-[(morpholine-4-carbonyl)-amino]-pyridin-4-ylmethyl}-amino)-benzoic acid methyl ester

[0112]



2-({2-[(Morpholine-4-carbonyl)-amino]-pyridin-4-ylmethyl}-amino)-benzoic acid methyl ester was prepared from 2-[(2-bromo-pyridin-4-ylmethyl)-amino]-benzoic acid methyl ester and morpholine-4-carboxylic acid amide in analogy to the procedures detailed in W02004/01302; ¹H-NMR (300 MHz, d₆-DMSO) 9.19 (1H, s), 8.15-8.19 (2H, m), 7.79-7.84 (2H, m), 7.29-7.34 (1H, m), 6.92 (1H, dd), 6.56-6.62 (2H, m), 4.50 (2H, d), 3.83 (3H, s), 3.57-3.60 (4H, m), 3.42-3.46 (4H, m).

[0113] The following examples detail the biological activity and use of the compounds of the invention without the scope of the claimed compounds being limited to these examples.

KDR Kinase Inhibition

[0114] Kinase activity was measured with a GST-kinase domain fusion construct of the KDR kinase according to the following protocol to obtain concentration response curves. Components were added into a microtiterplate in the following sequence: 10 μl of inhibitor in threefold final concentration [3% DMSO in buffer (40 mM TrisCl pH 7.5; 1 mM DTT, 1 mM MnCl₂, 10 mM MgCl₂, 2.5 Promille Polyethyleneglycol 20000)] and 10 μl of substrate mixture [24 μM ATP, 24 μg/ml poly (Glu₄Tyr) in buffer, specific activity approx. 500 cpm/pmol ³²P-γATP]. Reaction was started by adding 10 μl of enzyme preparation diluted appropriately in buffer that contains 10 μM vanadate. After incubation for exactly 10 min the reaction

was stopped by adding of 10 μ l stop solution (250mM EDTA). 10 μ l of the reaction mixture were transferred to phosphocellulose filters. The filters were washed in 0.1% phosphoric acid, dried before meltilex scintillator was applied (Wallac, Perkin-Elmer) and the radioactivity was counted.

5 VEGFR-3 Autophosphorylation

[0115] MVECs (1.5×10^6 /well) of a low passage number were plated on collagen-G coated 48 well plates in EBM complete medium (including EGM-2, BD-Clonetechn). 5h later, medium was exchanged for EBM-2 without EGM-2 but containing 0.2% BSA (EBM meager). 12 h later medium was removed, 250 μ l EBM-2 meager and the respective compound dilutions were added in 50 μ l EBM-2 meager. Solutions were carefully mixed and left for 5 min at 4°C before the addition of 200 μ l EBM-2 meager containing VEGF-C (final concentration in the assay is 5 nM; Reliatech, Braunschweig). The solution was then carefully mixed and incubated for 15 min at room temperature. The medium was removed and cells were washed twice with cold PBS/2mM vanadate. Cells were then lysed with 100 μ l Duschl buffer [50mM Hepes pH 7.2; 150 mM NaCl; 1 mM $MgCl_2$; 1.5% Triton X-100; 10 mM Na-Pyrophosphate; 100 mM Na-Fluoride; 10% glycerol + (freshly added before the experiment) 2 mM Orthovanadate and 1 tablet per 50 ml Complete (Roche # 1836145)]

[0116] For the ELISA, Fluoronic MaxiSorp - MTP plates (# 3204006 Zinser)- were coated overnight at 4°C with Flt-4 antibody (Flt-4 (C-20) # sc-321 Santa Cruz); 1 μ g/ml in coating buffer: Na_2CO_3 pH 9.6 100 μ l/well). After 3x washing with washing buffer (0.1% Tween 20 in Na_2HPO_4 pH 7.4) the wells were incubated with 250 μ l blocking buffer (Roti Block 1/10 from Roth, Karlsruhe for 1 h at room temperature). 3x washing with washing buffer was followed by addition of cell lysates and incubation over night at 4°C. Then wells were washed 3x, anti-phosphotyrosine antibody coupled to HRP (16-105; UPSTATE; dilution 1/20000 in TBST+3% Top Block # 37766, Fluka) was added and incubated overnight at 4°C. Washing with washing buffer (6x) preceded the addition of BM chemoluminescence ELISA reagent # 1582950 (Roche) and measurement of luminescence.

25 Cytochrome P450 Inhibition

[0117] The Cytochrome P450 isoenzyme inhibition was performed according to the publication of Crespi *et al.* (Anal. Biochem., 1997, 248, 188-190) with use of the baculovirus/insect cell-expressed, human Cytochrome P 450 isoenzymes (2C9 and 2C19).

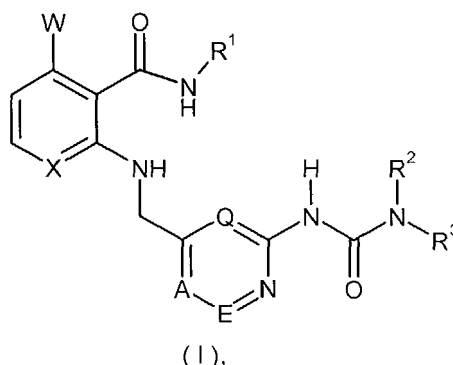
[0118] Selected results are presented in the following table:

Example	IC50 KDR-Kinase (VEGFR-2) (nM)	IC50 CYP 2C9 (μ M)	IC50 CYP 2C19 (μ M)
3.30 from WO 04/13102	10	0.9	1.7
3.40 from WO 04/13102	40	1.1	2.3
3.41 from WO 04/13102	27	5.7	1.5
1.1	20	16.0	27.0
1.2	17	19.0	12.0
3.0	29	4.4	8.9
3.6	29	13.0	9.0

[0119] The advantages of the compounds of the invention compared to known compounds can be readily demonstrated by the above studies.

Claims

1. A compound of formula (I),



wherein:

X is CH or N;

W is hydrogen or fluorine;

A, E and Q independently of one another, are CH or N, whereby only a maximum of two nitrogen atoms are contained in the ring;

R¹ is aryl or heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸;

R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain further heteroatoms and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶ whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl;

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl;

R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl or -NR⁷R⁸;

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

2. A compound as claimed in claim 1, wherein X is CH.

3. A compound as claimed in any one of claims 1 or 2, wherein W is hydrogen.

4. A compound as claimed in any one of claims 1-3, wherein A, E, and Q each are CH.

5. A compound as claimed in claim 1, wherein X is CH, W is hydrogen, and A, E, and Q each are CH.

6. A compound as claimed in any one of claims 1-5, wherein R¹ is heteroaryl optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸.

7. A compound as claimed in any one of claims 1-5, wherein R¹ is heteroaryl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸.

8. A compound as claimed in any one of claims 1-5, wherein R¹ is quinolinyl, isoquinolinyl, or indazolyl which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸.
9. A compound as claimed in any one of claims 1-5, wherein R¹ is quinolinyl, isoquinolinyl, or indazolyl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸.
10. A compound as claimed in any one of claims 1-5, wherein R¹ is indazolyl substituted with C₁-C₁₂-alkyl.
11. A compound as claimed in any one of claims 1-5, wherein R¹ is 2-methyl-indazolyl or 1-methyl-indazolyl.
12. A compound as claimed in any one of claims 1-11, wherein R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which contains no or one further heteroatom and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶, or -CO₂R⁶, whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵.
13. A compound as claimed in any one of claims 1-12, wherein R⁴ is C₁-C₁₂-alkyl.
14. A compound as claimed in any one of claims 1-12, wherein R⁴ is -CH₃.
15. A compound as claimed in any one of claims 1-14, wherein R⁵ is -CH₃ or hydrogen.
16. A compound as claimed in any one of claims 1-14, wherein R⁵ is hydrogen.
17. A compound as claimed in any one of claims 1-16, wherein R⁶ is C₁-C₁₂-alkyl or -NR⁷R⁸.
18. A compound as claimed in any one of claims 1-16, wherein R⁶ is C₁-C₁₂-alkyl.
19. A compound as claimed in any one of claims 1-16, wherein R⁶ is -CH₃.
20. A compound as claimed in any one of claims 1-19, wherein R⁷ and R⁸ independently of one another, are hydrogen, -COR⁶, -SO₂R⁶, or C₁-C₁₂-alkyl.
21. A compound as claimed in any one of claims 1-19, wherein R⁷ and R⁸ independently of one another, are hydrogen or -CH₃.
22. A compound as claimed in claim 1, wherein:
- X is CH;
W is hydrogen;
A, E and Q each are CH;
R¹ is aryl or heteroaryl, which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸;
R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain further heteroatoms and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶ whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;
R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl;
R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl;
R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl or -NR⁷R⁸;
R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl,

halo-C₁-C₁₂-alkyl or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

- 23.** A compound as claimed in claim 1,
wherein:

X is CH;

W is hydrogen;

A, E and Q each are CH;

R¹ heteroaryl substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸;

R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain further heteroatoms and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶ whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl;

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl;

R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl or -NR⁷R⁸,

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

- 24.** A compound as claimed in claim 1,
wherein:

X is CH;

W is hydrogen;

A, E and Q each are CH;

R¹ is quinolinyl, isoquinolinyl, or indazolyl which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸;

R² and R³ together with the nitrogen atom form a 3-8 membered heterocycloalkyl ring, which may optionally contain further heteroatoms and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶ whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl;

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl;

R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl or -NR⁷R⁸;

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

25. A compound as claimed in claim 1,
wherein:

X is CH;

W is hydrogen;

A, E and Q each are CH;

R¹ is quinolinyl, isoquinolinyl, or indazolyl which is substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸;

R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which may optionally contain further heteroatoms and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶ whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl;

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl;

R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl or -NR⁷R⁸;

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

26. A compound as claimed in claim 1,
wherein:

X is CH;

W is hydrogen;

A, E and Q each are CH;

R¹ is indazolyl which may be optionally substituted in one or more places in the same way or differently with halogen, hydroxy, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -SO₂R⁶, -OR⁵, -SOR⁴, -COR⁶, -CO₂R⁶ or -NR⁷R⁸, whereby C₁-C₁₂-alkyl may be substituted with -NR⁷R⁸;

R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which may optionally contain further heteroatoms and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶ whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, aryl or heteroaryl;

R⁵ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl or halo-C₁-C₆-alkyl;

R⁶ is hydrogen, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, halo-C₁-C₆-alkyl, aryl or -NR⁷R⁸;

R⁷ and R⁸ independently of one another, are hydrogen, -SO₂R⁶, -COR⁶, aryl, C₃-C₈-cycloalkyl, C₁-C₁₂-alkyl, halo-C₁-C₁₂-alkyl or C₁-C₁₂-alkoxy, whereby C₁-C₁₂-alkyl may be optionally substituted with -OR⁵ or -N(CH₃)₂, or R⁷ and R⁸ may also be chosen in such a way as to provide a 3-8 membered cycloalkyl ring, which may optionally contain further heteroatoms and may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, =O, -OR⁵, -COR⁶, -SR⁴, -SOR⁴ or -SO₂R⁶; and

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

27. A compound as claimed in claim 1,
wherein:

X is CH;

W is hydrogen;

A, E and Q each are CH;

R¹ is indazolyl substituted with C₁-C₁₂-alkyl;

R² and R³ together with the nitrogen atom form a 5 or 6 membered heterocycloalkyl ring, which may optionally contain further heteroatoms and which may be optionally substituted in one or more places in the same way or differently with halogen, cyano, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, halo-C₁-C₆-alkyl, C₁-C₃-dialkyl ketal, C₁-C₃-cyclic ketal, =O, -OR⁵, -SR⁴, -SOR⁴, -SO₂R⁶, -COR⁶ or -CO₂R⁶ whereby C₁-C₁₂ alkyl optionally can also be substituted with a group -OR⁵;

R⁴ is C₁-C₁₂-alkyl;

R⁵ is hydrogen;

R⁶ is C₁-C₁₂-alkyl; and,

as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

28. A compound as claimed in claim 1, selected from the group consisting of:

4-hydroxy-4-methyl-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-hydroxy-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-hydroxy-4-trifluoromethyl-piperidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

1-oxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

1,1-dioxo-thiomorpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-methyl-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-methyl-piperazine-1-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

4-methanesulfonyl-piperazine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(7-methoxy-isoquinolin-3-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

2,6-dimethyl-morpholine-4-carboxylic acid (4-[[2-(1-methyl-1H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

2,6-dimethyl-morpholine-4-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

3-hydroxy-pyrrolidine-1-carboxylic acid (4-[[2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[3-fluoro-2-(2-methyl-2H-indazol-6-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

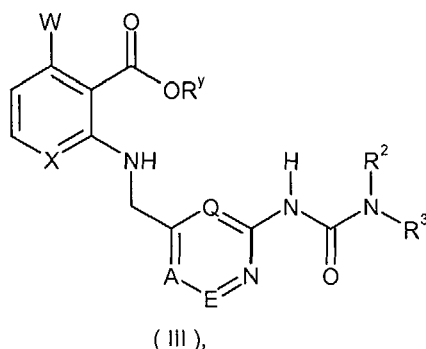
morpholine-4-carboxylic acid (4-[[2-(isoquinolin-3-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

morpholine-4-carboxylic acid (4-[[2-(3,6-difluoro-quinolin-2-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide, and

morpholine-4-carboxylic acid (4-[[2-(3-fluoro-6-methoxy-quinolin-2-ylcarbamoyl)-phenylamino]-methyl]-pyridin-2-yl)-amide,

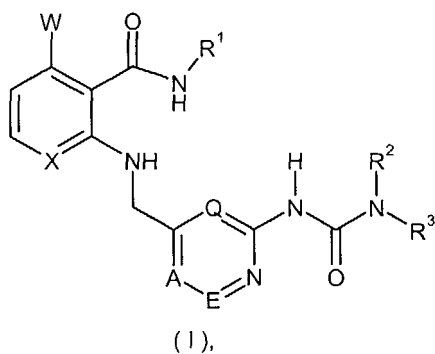
as well as isomers, diastereoisomers, enantiomers, tautomers and salts thereof.

29. A pharmaceutical agent comprising at least one compound of formula (I) according to any one of claims 1 to 28.
30. A pharmaceutical agent comprising at least one compound of formula (I) according to any one of claims 1 to 28 and at least one pharmaceutically acceptable carrier.
31. A pharmaceutical agent according to claims 29 or 30 for use in the treatment of diseases associated with persistent angiogenesis and/or diseases associated with excessive lymphangiogenesis.
32. A pharmaceutical agent according to claims 29 or 30 for use in the treatment of tumor- or metastases-growth; psoriasis; Kaposi's sarcoma; restenosis including stent-induced restenosis; Crohn's disease; Hodgkin's disease; leukemia; arthritis including rheumatoid arthritis, hemangioma, angiofibroma; endometriosis; eye diseases including diabetic retinopathy, neovascular glaucoma; corneal transplants; renal diseases, including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathic syndrome, transplant rejections and glomerulopathy; fibrotic diseases, including cirrhosis of the liver; mesangial cell proliferative diseases; arteriosclerosis; injuries to the nerve tissue, and for inhibiting the reocclusion of vessels after balloon catheter treatment; in vascular prosthetics or after mechanical devices are used to keep vessels open, as immunosuppressive agent for supporting scar-free healing; senile keratosis; contact dermatitis; and asthma.
33. A pharmaceutical agent according to claim 29 or 30 for use as VEGF receptor kinase 3-inhibitors of lymphangiogenesis.
34. A compound of formula (I) according to any one of claims 1 to 28 for use in a method for the treatment of the human or animal body.
35. A compound of formula (I) according to any one of claims 1 to 28 for use in the preparation of a pharmaceutical product for the treatment of a disease for which an inhibition of angiogenesis and/or lymphangiogenesis and/or the VEGF receptor kinases is beneficial.
36. A compound of formula (I) according to any one of claims 1 to 28 for use as an inhibitor of the tyrosine kinases VEGFR-1 and VEGFR-2.
37. A compound of general formula (III),

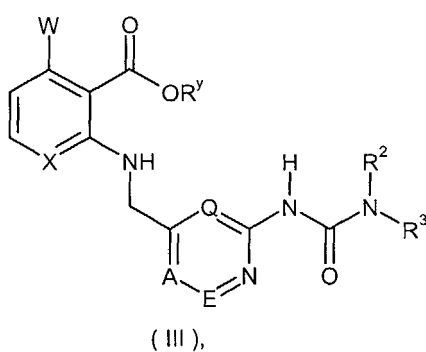


in which A, E, Q, W, X, R² and R³, are as defined in formula (I) and R^y is H or C₁-C₆-alkyl, as intermediate for the preparation of a compound of formula (I).

38. A compound as claimed in claim 37, wherein R^y is H or C₁-C₂-alkyl.
39. The use of a compound as claimed in any one of claims 37 or 38, as intermediate for the preparation of a compound of formula (I).
40. A process for the preparation of a compound of formula (I),

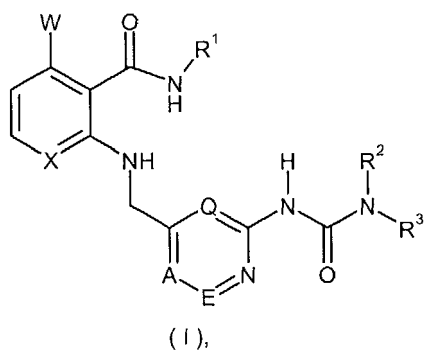


wherein all substituents are as described in claim 1, in which a compound of formula (III),

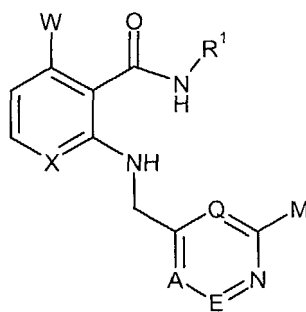


as defined in any one of claims 37 or 38, is reacted with an amine of formula R^1NH_2 in which R^1 is as defined in claim 1.

41. A process for the preparation of a compound of formula (I),



wherein all substituents are as described in claim 1, in which a compound of formula (II),



(II),

wherein A, E, Q, W, X, and R¹ are as defined in claim 1 and M stands for halogen, is:

- (i) first converted to an amine and subsequently converted to a compound of formula (I) by reaction with a carbamoyl chloride of formula ClCONR²R³, wherein R² and R³ are as defined in claim 1; or alternatively,
- (ii) reacted with a compound of formula H₂NCONR²R³, wherein R² and R³ are as defined in claim 1; or alternatively,
- (iii) first converted to an amine, then converted to a compound of formula (I) by first reacting with a compound of formula ClCO₂Ph and then reacting with a compound of formula HNR²R³, wherein R² and R³ are as defined in claim 1.

42. A process as claimed in claim 41, wherein in which the compound of formula (II) is reacted with a compound of formula H₂NCONR²R³, wherein R² and R³ are as defined in claim 1.



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 04 09 0418

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,X	WO 2004/013102 A (SCHERING AKTIENGESELLSCHAFT) 12 February 2004 (2004-02-12) examples 3.30,3.40,3.41 -----	1-42	C07D401/14 C07D401/12 C07D491/10 A61K31/44 A61P35/00
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			C07D
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 2 June 2005	Examiner Steendijk, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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